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Niacin as a potential AIDS preventive factor

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Summary A pentad of findings consistent with niacin depletion have been described in patients with AIDS. There are also clinical and laboratory data to support the potential benefit of niacin in HIV infection. In this paper, it is hypothesized that HIV infection induces niacin depletion, and that therapeutic niacin will act as an AIDS preventive factor. While viral inhibition is incontrovertibly the primary 'AIDS preventive factor', costly antiretroviral medications are simply out of reach for the majority of the world's HIV-infected people. Along with antiviral research, investigation must go forward to look at strategies to overcome the massive metabolic disruption caused by the production of approximately one billion virus particles per day. Niacin, the same B complex vitamin found in the early part of this century to be the 'pellagra preventive factor', is proposed here as a secondary 'AIDS preventive factor' in HIV-infected persons. © 1999 Harcourt Publishers Ltd

INTRODUCTION

This hypothesis is built on three related concepts: (1) niacin depletion in the absence of dietary deficiency; (2) infection-induced vitamin depletion; and (3) improved clinical outcome associated with therapeutic use of vitamins during infection. All three of these concepts have proofs of principle independent of the HIV pandemic. Carcinoid syndrome can lead to niacin depletion in the absence of dietary deficiency (1). In carcinoid syndrome, the body's tryptophan is diverted by tumor metabolism from niacin production towards serotonin production, this shunting leading to pellagra in some carcinoid patients (2). Infection-associated vitamin depletion and beneficial therapeutic vitamin use during infection have both been demonstrated with vitamin A during measles infection (3). The natural history of HIV infection is a state of progressive immune dysfunction occurring over a number of years and culminating in the clinical state of acquired immune deficiency syndrome (AIDS) (4). This syndrome has a number of poorly understood phenomena associated with it which have not been explained by direct viral effects and are hypothesized here to be a result of HIV-induced niacin depletion. If therapeutic niacin finds a place as an AIDS preventive factor, this might then be a starting point for hope of affordable interventions in the developing world (5).

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NIACIN

Niacin was identified as the pellagra preventive factor through the work of Joseph Goldberger and others (6). Despite prevailing theories of an infectious etiology, vitamin deficiency was ultimately proven to be the causative problem in epidemic pellagra (7). Since the 1930s, the biochemical basis of this problem has been clarified, and the list of etiologies has expanded beyond dietary deficiency to include drug-induced pellagra, pellagra induced by inborn metabolic errors, and disease-associated pellagra (8).

Niacin, or vitamin B3, is the accepted name for two related vitamin compounds: nicotinic acid [NA] and nicotinamide [NAm]. Niacin's metabolic fate is the synthesis of nicotinamide nucleotide compounds such as nicotinamide adenine dinucleotide [NAD] (9). NAm, unlike NA, can be cleaved from and then recycled back to nicotinamide nucleotides in vivo through the action of NAD hydrolases (9).

There are four biosynthetic pathways for NAD. Two of the pathways utilize NAm as the initial precursor, one starts with NA, and the final synthetic pathway starts with tryptophan. These biosynthetic pathways are each dependent on a series of enzymatic steps, and there is significant variability in the tissue distribution of the

EXHIBIT C

enzymes. The pathway with the widest tissue distribution is one of the two NAm-associated pathways (9).

TRYPTOPHAN

The essential amino acid tryptophan is critical to the understanding of pellagra. Dietary tryptophan's metabolic fate is threefold: (1) protein synthesis; (2) serotonin synthesis; (3) oxidative metabolism (10). In normal individuals, the body uses only 5% of tryptophan for the seratonin and protein synthesis pathways, and disposes of the remaining tryptophan along the kynurenine pathway, where the end products are either nicotinamide nucleotides or acetylCoA (10). The considerable volume of data on increased quinolinic acid in HIV infection suggests that increased conversion to nicotinamide nucleotides is occurring in HIV infection (11). Normally, approximately 1 in every 60 tryptophan molecules is converted to niacin (12). This understanding has led to the use of the term 'niacin equivalents[NES]' to describe total dietary intake of niacin as the sum of both vitamin intake and tryptophan-related synthesis.

PELLAGRA: A PENTAD

The three Ds of dermatitis, diarrhea, and dementia clinically identify pellagra. This handy mnemonic is confounded by clinical data which suggest that in pellagrins the full clinical triad is only present in a minority of cases (13). Spivak and Jackson found that only 22% of pellagrins in their series had the full triad. Even dermatitis, often anticipated as the sine qua non, was absent in 15% of historical cases reviewed (13).

The biochemical findings associated with pellagra have been known for some time (8). Although direct measures of serum niacin are possible, the work of Fu et al. suggests that the serum tryptophan and intracellular NAD are reliable measures of niacin depletion. In Fu's study, moderate niacin deficiency led to intracellular NAD decreases, while more severe niacin deficiency led to both intracellular NAD and serum tryptophan decreases (14). None of the subjects in Fu's study was reported to have developed clinical signs of dermatitis, diarrhea, or dementia during a five-week period of dietary niacin deficiency, suggesting that biochemical changes are a more sensitive monitor than clinical signs. Pellagra is marked by a total of five findings: dermatitis, diarrhea, dementia, decreased cellular NAD, and decreased serum tryptophan.

AIDS AND THE 3 Ds

Amongst a number of poorly understood clinical findings in AIDS patients are 'seborrheic' dermatitis, AIDS enteropathy, and AIDS dementia complex (ADC). The dermatitis is usually referred to as 'seborrheic' on the basis of clinical appearance, but the histology in AIDS is felt to be atypical (15). AIDS enteropathy is viewed as a diagnosis of exclusion in seropositive patients with chronic diarrhea, who have no infectious cause determined after complete evaluation (16). Mucosal histopathology is remarkable for low-grade atrophy and a maturational defect in the enterocytes (17). ADC is marked pathologically by neuronal loss (18), and microglial nodules (19). With all three of these problems, scientists and clinicians have tried with only limited success to link the changes in the skin, mucosa, and the brain with localized presence of the virus itself. Recent reports associating the attenuation of two of these conditions with the use of highly active antiretroviral therapy[HAART] (20,21) suggest that the three Ds may be metabolic effects of viral production.

NAD AND TRYPTOPHAN IN HIV INFECTION

Cellular NAD depletion occurs in HIV-infected patients in T4 lymphocytes, T8 lymphocytes, and non-T lymphocytes (22). This depletion occurs in a progressive manner with advancing HIV disease. Lymphocytes from symptomatic HIV-infected patients have an impaired ability to produce NAD when stimulated (23). Along with these clinical observations are two in vitro observations that demonstrate that: (1) acute infection with HIV leads to a rapid decrease in NAD concentration (24); and (2) chronic infection with HIV leads to chronic depression of NAD concentration (25).

Numerous groups have observed decreased serum tryptophan levels in patients with HIV infection (26,27). It has also been observed that there are increased levels of intermediates of tryptophan oxidative metabolism along the NAD biosynthetic pathway (28). Recently, the observed depression of tryptophan levels have been shown to rebound with antiviral therapy (29).

These data, when taken together, suggest a metabolic shunting of tryptophan towards NAD synthesis in response to a virus-induced NAD depletion. If Fu's data apply, then the presence of both intracellular NAD depletion and serum tryptophan depletion suggests significant niacin depletion (14).

EVIDENCE FOR BENEFITS OF NIACIN IN HIV INFECTION

In vitro data demonstrate that niacin in the form of NAm acts as an inhibitor of HIV infection (30). This inhibition occurs in both acute and chronic infection models at millimolar concentrations. The inhibition takes place, at least in part, at a post-integrational step in the viral life-

cycle (30). It was also noted that this same compund, NAm, leads to an increase in intracellular NAD when added to infected cultures, a response that is otherwise impaired in HIV-infected cells (23,24).

There are no published data on the prospective use of therapeutic niacin to inhibit HIV in vivo. There have been two prospective observational studies, however, where increased dietary niacin was associated with improved clinical outcome (31,32). This correlation was statistically significant in the study by Tang and colleagues, who found that niacin intake exceeding 64 mg per day coincided with decreased risk of HIV disease progression and improved survival (32). This amount of niacin is only two to four times what the average diet provides (12). Its important to note that Tang's study also found survival benefit with some other vitamin compounds including vitamin B6. Pertinent to this discussion is the fact that vitamin B6 is a necessary cofactor in the conversion of tryptophan to NAD (33).

NIACIN DEPLETION: A QUESTION OF SUPPLY AND DEMAND

A mechanism for niacin depletion in HIV infection is not clear at this time. It is apparent that, in order of HIV to induce niacin depletion, there must be either a change in supply, demand or both (supply and demand) in the HIV-infected state. Since there are no stored niacin reserves in the body, niacin requirements are met by ingestion of the vitamin and the de novo synthesis from dietary tryptophan (13). Examination of dietary intake in HIV-infected individuals has failed to suggest specific deficiency in either NE or tryptophan (34). As discussed, there is a body of evidence which suggests that tryptophan's conversion to nicotinamide nucleotides is activated in the HIV-infected state (11,28). This increase in tryptophan oxidation makes undersupply of niacin an unlikely culprit in niacin depletion, unless there is a heretofore unidentified block in the pathway which converts tryptophan to NAD. Any suggestion of simply increasing dietary tryptophan should be viewed with caution given the potential for side-effects (35).

Overutilization of niacin seems more likely than undersupply, given the observation that HIV infection induces induces NAD depletion (23). In vitro data suggest that this is a direct effect of HIV on cellular NAD levels (24,25). The depletion of NAD, multiplied by the more than one billion T lymphocytes turned over per day during HIV infection and stretched over a period of several years could readily be expected to cause niacin depletion (4). NAD, the biologic end product of niacin, is depleted on a intracellular level by HIV and this implies that systemic niacin depletion is primarily tied to niacin overutilization in HIV-infected patients.

CD38: A POTENTIAL CLUE TO NIACIN DEPLETION

CD38 is a NAD hydrolase on the cell surface which catalyzes the conversion of extracellular NAD to NAm and ADP-ribose (36). Both CD4 and CD8 lymphocytes demonstrate an increeased percentage of cells positive for CD38 with HIV seroconversion (37). CD38 numbers keep increasing in T lymphocytes with advancing HIV disease (38). Mehta et al. suggested that the changes in CD38+ population during disease progression imply that CD38 is endowed with 'peculiar protective function' (36). CD38 allows extracellular NAD, which can not enter intact cells, to be cleaved on the surface, thereby increasing NAm in the extracellular microenvironment. This NAm can then enter the cell and form NAD (39). CD38's ectoenzyme activity and the resultant increase in extracellular niacin are the likely explanations for the finding by Skurnik et al. that serum niacin levels increase with HIV infection (40). CD38 activity may also contribute to the T8 lymphocyte's antiviral activity since the NAm released has potential antiviral activity (30,41).

The importance of CD38 in HIV infection is becoming increasingly appreciated. CD38 was shown to be a stronger predictor of AIDS and death in HIV infection than CD4 counts in one study (42). CD38 numbers decrease with HAART, suggesting that control of HIV infection leads to diminished signaling for CD38 upregulation (43). We need to understand the role of CD38 in HIV infection more completely before the details of HIV-induced niacin metabolism can be fully understood.

CONCLUSION

This hypothesis, if supported by further study, may provide some hope to the 90% of the world's HIV-infected population who live beyond the reach of costly antiretroviral therapies (5). Niacin may also find a place as an adjunct to HAART. Clinical trials of niacin as an AIDS preventive factor are warranted by the follwoing:

1. the clinical observation that a modest increase in dietary niacin is coincident with decreased risk for progression to AIDS or death in patients with HIV;
2. in vitro data showing niacin to be an inhibitor of HIV production;
3. the pentad of poorly explained phenomena in AIDS patients which conicides with the five characteristic findings in niacin depletion, i.e. (a) dermatitis; (b) diarrhea; (c) dementia; (d) intracellular NAD depletion; (e) serum tryptophan depletion;
4. the safety profile of niacin as a drug (44).
5. the wide availability of inexpensive niacin.

It will likely require a large trial group over a prolonged period in order to prove niacin therapy to be a useful

AIDS preventive factor. The chance of demonstrating this effect in Europe or the USA, where expensive antivirals have become the standard of care, may be difficult but, in the developing world, where scarce resources cry out for inexpensive therapeutic compounds, the time may be right for clincial trials of therapeutic niacin. Meanwhile, further study is necessary to delineate the metabolic details of HIV-induced niacin depletion.

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